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ORIGINAL REPORT

Neurocognitive Outcomes Decades After Treatment for Childhood Acute Lymphoblastic Leukemia: A Report From the St Jude Lifetime Cohort Study

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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ABSTRACT

Purpose
To determine rates, patterns, and predictors of neurocognitive impairment in adults decades after treatment for childhood acute lymphoblastic leukemia (ALL).

Patients and Methods
Survivors of childhood ALL treated at St Jude Children's Research Hospital who were still alive at 10 or more years after diagnosis and were age ≥ 18 years were recruited for neurocognitive testing. In all, 1,014 survivors were eligible, 738 (72.8%) agreed to participate, and 567 (76.8%) of these were evaluated. Mean age was 33 years; mean time since diagnosis was 26 years. Medical record abstraction was performed for data on doses of cranial radiation therapy (CRT) and cumulative chemotherapy. Multivariable modeling was conducted and glmulti package was used to select the best model with minimum Akaike information criterion.

Results
Impairment rates across neurocognitive domains ranged from 28.6% to 58.9%, and those treated with chemotherapy only demonstrated increased impairment in all domains (all P values $< .006$). In survivors who received no CRT, dexamethasone was associated with impaired attention (relative risk [RR], 2.12; 95% CI, 1.11 to 4.03) and executive function (RR, 2.42; 95% CI, 1.20 to 4.91). The impact of CRT was dependent on young age at diagnosis for intelligence, academic, and memory functions. Risk for executive function problems increased with survival time in a CRT dose-dependent fashion. In all survivors, self-reported behavior problems increased by 5% (RR, 1.05; 95% CI, 1.01 to 1.09) with each year from diagnosis. Impairment was associated with reduced educational attainment and unemployment.

Conclusion
This study demonstrates persistent and significant neurocognitive impairment in adult survivors of childhood ALL and warrants ongoing monitoring of brain health to facilitate successful adult development and to detect early onset of decline as survivors mature.

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INTRODUCTION

The survival rate of childhood cancer exceeds 80% with recent advances in treatment, such that one in 640 young adults in the United States is estimated to be a pediatric cancer survivor.[1] A proportion of these survivors experience treatment-related complications in health, behavior, and/or quality of life, and the majority receive general medical care, with infrequent coverage of cancer-related late effects.[2] Knowledge of the extent and specific pattern of these late effects may enhance long-term medical follow-up as survivors mature into adulthood.

Acute lymphoblastic leukemia (ALL) represents the largest diagnostic group of survivors of childhood cancer. Within this group, neurocognitive impairment is a common late effect widely attributed to cranial radiation therapy (CRT).[3] Controversy remains over CRT dose thresholds associated with impairment, and recent reports suggest little risk with doses ≤ 18 Gy or with chemotherapy treatment alone.[4-6] These studies have focused on young survivors less than 10 years from diagnosis, and there are no published reports comparing treatment exposure on direct neurocognitive assessments in survivors during middle adulthood. We previously reported high rates of

Table 1. Survivor Demographic and Treatment Characteristics

Characteristic	No CRT (n = 214)				18 Gy (n = 167)				24 Gy (n = 186)				Dates*	*P*
	No.	%	Mean	SD	No.	%	Mean	SD	No.	%	Mean	SD		
Demographics														
Sex														.73
Female	116	54.2			86	51.5			95	51.1				
Male	98	45.8			81	48.5			91	48.9				
Race/ethnicity														.005
White	197	92.1			146	87.4			180	96.8				
Other	17	7.9			21	12.6			6	3.2				
Highest education level														.62
< 12 years (ie, less than high school graduation)	22	10.3			19	11.4			28	15.1				
High school/GED	42	19.6			34	20.4			38	20.4				
Vocational training	7	3.3			6	3.6			16	8.6				
Some college	66	30.8			48	28.7			46	24.7				
College graduate	55	25.7			40	24.0			42	22.6				
Postgraduate level	15	7.0			17	10.2			13	7.0				
Current employment														.82
Full time	125	58.4			99	59.3			111	59.7				
Part time	33	15.4			22	13.2			18	9.7				
Unemployed	36	16.8			38	22.8			52	28.0				
Student/homemaker	20	9.4			8	4.8			5	2.7				
Current age, years			27.8	5.1			31.5	5.8			39.1	6.2		< .001
Treatment characteristics														
Age at diagnosis, years			6.9	4.2			6.6	4.6			6.3	4.3		.38
Time since diagnosis, years			20.9	5.5			24.9	5.1			32.8	5.4		< .001
Methotrexate†														
IT, mL			169.5	61.2			167.2	82.2			85.0	79.8		< .001
IV, g/m^2			14.2	8.0			4.0	5.0			2.4	2.8		< .001
HD IV g/m^2			13.0	7.6			3.5	4.8			0.7	2.8		< .001
Treatment protocol number														
Total therapy 2, 3, 4	—	—			3	1.8			—	—			1962-1966	
Total therapy 5, 6, 7	—	—			3	1.8			33	17.7			1967-1971	
Total therapy 8, 9	—	—			8	4.8			110	59.1			1972-1979	
Total therapy 10	49	22.9			46	27.5			16	8.6			1979-1983	
Total therapy 11	45	21.0			84	50.3			17	9.1			1984-1988	
Total therapy 12	34	15.9			10	6.0			3	1.6			1988-1991	
Total therapy 13	71	33.2			10	6.0			2	1.1			1991-1994	
Other	15	7.0			3	1.8			5	2.7				

Abbreviations: CRT, cranial radiation therapy; GED, General Educational Development; HD, high density; IT, intrathecal; IV, intravenous; SD, standard deviation.
*Dates of treatment protocols entered in calendar years; overlapping years reflect treatment transition within that year.
†Cumulative doses are listed for IT and IV methotrexate. HD IV methotrexate was calculated separately. HD IV methotrexate was defined as daily dose of ≥ 1 g/m^2 IV methotrexate.

neurocognitive impairment in ALL survivors during adolescence.[7] Since brain development continues well into adulthood, the extent of impairment may change as survivors mature. Understanding patterns and risk for impairment during adulthood is important because impairment has an impact on major life functions. Neurocognitive impairment in adult survivors of childhood cancer has been linked to employment,[8] independent living,[9] and health care use.[10]

To the best of our knowledge, this is the first comprehensive examination of neurocognitive outcomes in a large cohort of adult survivors of childhood ALL. We provide data on rates and patterns of impairment, covering breadth and depth of functional limitations, including functions relevant to success as an adult. We examine associations between these outcomes and educational attainment and employment. We hypothesized that higher doses of CRT would be related to impairment and age at diagnosis and that time since diagnosis and sex would moderate the impact. We also expected that methotrexate and glucocorticoids would be associated with impairment in patients who did not receive CRT. Finally, we expected that neurocognitive impairment would have an adverse impact on educational attainment and employment.

PATIENTS AND METHODS

Study Population

Potential participants were identified from a sample of 1,219 survivors of ALL treated at St Jude Children's Research Hospital (SJCRH) between 1962 and 1999 and registered in the St Jude Lifetime Cohort Study (SJLIFE; for a detailed description of this study, see Hudson et al[11]). All survivors provided written informed consent and the protocol was approved by the institutional review board. Eligibility criteria included current age ≥ 18 years and being 10 or more years from diagnosis. Exclusion criteria included history of developmental disorder or neurologic event unrelated to cancer and relapse or subsequent malignancy. Survivors treated with bone marrow transplantation were

Table 2. Degree of Neurocognitive Impairment in Adult Survivors of Childhood ALL

Domain/Specific Ability	Mean	SD	Impairment: None No.	None %	None 95% CI	Mild No.	Mild %	Mild 95% CI	Moderate No.	Moderate %	Moderate 95% CI	Severe No.	Severe %	Severe 95% CI
Intelligence			364	64.3	60.4 to 68.3	77	13.6	10.8 to 16.4	35	6.2	4.2 to 8.2	90	15.9	12.9 to 18.9
Full scale	−0.3	1.0	447	79.1	75.8 to 82.5	54	9.6	7.1 to 12.0	28	5.0	3.2 to 6.7	36	6.4	4.4 to 8.4
Verbal	−0.5	1.1	383	67.5	63.7 to 71.4	74	13.1	10.3 to 15.8	36	6.3	4.3 to 8.4	74	13.1	10.3 to 15.8
Perceptual	−0.0	1.0	490	86.7	83.9 to 89.5	20	3.5	2.0 to 5.1	12	2.1	0.9 to 3.3	43	7.6	5.4 to 9.8
Academics			364	65.1	61.2 to 69.1	94	16.8	13.7 to 19.9	45	8.1	5.8 to 10.3	56	10.0	7.5 to 12.5
Word reading	−0.4	0.7	479	85.5	82.6 to 88.4	38	6.8	4.7 to 8.9	24	4.3	2.6 to 6.0	19	3.4	1.9 to 4.9
Mathematics	−0.6	1.0	382	68.7	64.9 to 72.6	86	15.5	12.5 to 18.5	39	7.0	4.9 to 9.1	49	8.8	6.5 to 11.2
Attention			329	58.8	54.7 to 62.8	70	12.5	9.8 to 15.2	38	6.8	4.7 to 8.9	123	22.0	18.5 to 25.4
Focus	−0.2	1.4	457	81.0	77.8 to 84.3	31	5.5	3.6 to 7.4	18	3.2	1.7 to 4.6	58	10.3	7.8 to 12.8
Sustained	−0.5	2.2	448	80.1	76.8 to 83.5	23	4.1	2.5 to 5.8	13	2.3	1.1 to 3.6	75	13.4	10.6 to 16.2
Variability	−0.4	1.3	418	74.8	71.2 to 78.4	51	9.1	6.7 to 11.5	34	6.1	4.1 to 8.1	56	10.0	7.5 to 12.5
Memory			250	44.2	40.1 to 48.3	147	26.0	22.4 to 29.6	53	9.4	7.0 to 11.8	116	20.5	17.2 to 23.8
New learning	−0.2	1.2	435	76.9	73.4 to 80.3	54	9.5	7.1 to 12.0	19	3.4	1.9 to 4.8	58	10.2	7.7 to 12.7
Short-term recall	−0.3	1.2	389	68.7	64.9 to 72.5	79	14.0	11.1 to 16.8	33	5.8	3.9 to 7.8	65	11.5	8.9 to 14.1
Long-term recall	−0.4	1.3	364	64.3	60.4 to 68.3	79	14.0	11.1 to 16.8	57	10.1	7.6 to 12.5	66	11.7	9.0 to 14.3
Span	−0.3	1.1	381	67.2	63.3 to 71.1	135	23.8	20.3 to 27.3	13	2.3	1.1 to 3.5	38	6.7	4.6 to 8.8
Processing speed			247	43.7	39.6 to 47.8	155	27.4	23.8 to 31.1	49	8.7	6.4 to 11.0	114	20.2	16.9 to 23.5
Motor	−1.0	1.4	331	58.6	54.5 to 62.6	85	15.0	12.1 to 18.0	41	7.3	5.1 to 9.4	108	19.1	15.9 to 22.4
Visual	−0.2	1.0	435	77.1	73.7 to 80.6	86	15.2	12.3 to 18.2	13	2.3	1.1 to 3.5	30	5.3	3.5 to 7.2
Visual-motor	−0.4	1.0	382	67.7	63.9 to 71.6	121	21.5	18.1 to 24.8	31	5.5	3.6 to 7.4	30	5.3	3.5 to 7.2
Executive function			232	41.1	37.0 to 45.1	144	25.5	21.9 to 29.1	58	10.3	7.8 to 12.8	131	23.2	19.7 to 26.7
Flexibility	−0.8	1.8	363	64.4	60.4 to 68.3	60	10.6	8.1 to 13.2	31	5.5	3.6 to 7.4	110	19.5	16.2 to 22.8
Fluency	−0.5	1.0	353	62.3	58.3 to 66.2	116	20.5	17.1 to 23.8	43	7.6	5.4 to 9.8	55	9.7	7.3 to 12.1
Working memory	−0.4	0.9	428	75.5	71.9 to 79.0	119	21.0	17.6 to 24.3	13	2.3	1.1 to 3.5	7	1.2	0.3 to 2.1
Behavior rating			402	71.4	67.7 to 75.1	58	10.3	7.8 to 12.8	39	6.9	4.8 to 9.0	64	11.4	8.7 to 14.0
Inhibition	−0.2	1.0	441	78.3	74.9 to 81.7	49	8.7	6.4 to 11.0	38	6.7	4.7 to 8.8	35	6.2	4.2 to 8.2
Shift	−0.4	1.2	381	67.7	63.8 to 71.5	70	12.4	9.7 to 15.2	48	8.5	6.2 to 10.8	64	11.4	8.7 to 14.0
Emotional control	−0.4	1.3	359	63.8	59.8 to 67.7	98	17.4	14.3 to 20.5	36	6.4	4.4 to 8.4	70	12.4	9.7 to 15.2
Self-monitor	−0.1	1.2	444	78.9	75.5 to 82.2	55	9.8	7.3 to 12.2	26	4.6	2.9 to 6.4	38	6.7	4.7 to 8.8
Cognitive rating			397	70.5	66.7 to 74.3	63	11.2	8.6 to 13.8	49	8.7	6.4 to 11.0	54	9.6	7.2 to 12.0
Initiation	−0.2	1.2	416	73.9	70.3 to 77.5	63	11.2	8.6 to 13.8	46	8.2	5.9 to 10.4	38	6.7	4.7 to 8.8
Working memory	−0.8	1.4	328	58.3	54.2 to 62.3	52	9.2	6.8 to 11.6	62	11.0	8.4 to 13.6	121	21.5	18.1 to 24.9
Planning	−0.2	1.1	412	73.2	69.5 to 76.8	63	11.2	8.6 to 13.8	43	7.6	5.4 to 9.8	45	8.0	5.8 to 10.2
Task completion	−0.3	1.2	409	72.6	69.0 to 76.3	53	9.4	7.0 to 11.8	60	10.7	8.1 to 13.2	41	7.3	5.1 to 9.4
Organization	−0.2	1.1	422	75.0	71.4 to 78.5	65	11.5	8.9 to 14.2	40	7.1	5.0 to 9.2	36	6.4	4.4 to 8.4

NOTE. Mean and SD presented in age-adjusted *z* scores, referenced to nationally representative norms. Age-adjusted *z* scores for impairment: none, > –1.0; mild, > –1.5 to –1.0; moderate, > –2.0 to –1.5; severe, ≤ –2.0.
Abbreviations: ALL, acute lymphoblastic leukemia; SD, standard deviation.

excluded. Of the 1,219 potential participants, 1,014 survivors were potentially eligible and 205 were excluded because of unrelated neurodevelopmental problems (Down syndrome, n = 8), relapse (n = 194), and second malignancy (n = 3). Potentially eligible survivors were randomly recruited in sequential blocks of 50 to facilitate evaluation of participants relative to possible selection. Of the 1,014 potentially eligible survivors, 738 (72.8%) agreed to participate. On the date the data were frozen for this analysis, 567 evaluable survivors (76.8%) had completed neurocognitive testing and 171 survivors had not yet completed their campus visits. No statistical differences were observed between the 567 participants and the 276 nonparticipants in current age ($P = .50$), race ($P = .64$), CRT dose ($P = .82$), age at diagnosis ($P = .81$), or decade of diagnosis ($P = .60$; Appendix Table A1, online only). Females represented a larger percentage of participants ($P = .02$).

Procedure

Medical record abstraction was performed to capture exposure data, including chemotherapy (cumulative doses), surgical procedures, and radiation (fields, doses, and beam energy). Comprehensive questionnaires covering health history and status, social and demographic factors, health behaviors, and psychosocial history were mailed to all participants.

Each participant underwent risk-based medical assessment consistent with the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers.[12] Assessment was based on primary diagnosis, age at diagnosis, and therapeutic interventions. Survivors treated with CRT and/or antimetabolite chemotherapy underwent neurocognitive assessment.

Neurocognitive testing was conducted during a 2-hour session in dedicated evaluation rooms. Assessed domains included intelligence,[13] academic skills,[14] attention,[15-17] memory,[18] processing speed,[15-17] and executive function.[15,16] Survivors completed a self-rating questionnaire to evaluate perceived neurobehavioral function, which has been validated in numerous studies of medical illness and neurologic injury and includes separate indices of behavioral and cognitive problems.[19] Order of testing was standardized, and survivors' schedules were adjusted to limit impact from fatigue and extraneous factors.

Statistical Analyses

Descriptive statistics were calculated for demographic and treatment characteristics and neurocognitive outcomes. The impact of CRT on neurocognitive outcomes was assessed by classifying survivors into three groups based on original treatment: chemotherapy only, 18-Gy CRT, and 24-Gy CRT.

Neurocognitive scores were transformed into age-adjusted z scores (mean, 0; standard deviation, 1.0) using national norms. Degree of neurocognitive impairment was defined by three thresholds based on z score: mild, more than –1.5 to −1.0; moderate, more than –2.0 to −1.5; severe, −2.0 or less. Frequency of impairment at each level was examined within the whole cohort, and group differences were compared by using severe impairment levels, as recommended by Binder et al,[19a] to reduce the likelihood of false-positive errors.

Multivariable modeling was conducted for each neurocognitive and patient-reported domain. The glmulti function of R software (R Foundation for Statistical Computing, Vienna, Austria) was used to select the best set of risk factors with minimum Akaike information criterion (AIC). Predictors included CRT group (24 Gy, 18 Gy, no CRT), age at diagnosis (continuous) and its interaction with CRT, time since diagnosis (continuous) and its interaction with CRT, sex and its interaction with CRT, intravenous (IV) methotrexate (per 1 g of cumulative exposure), and intrathecal (IT) methotrexate (per 50 mL of cumulative exposure). Model selection was based on logistic regression. The model based on the best AIC sometimes included risk factors that were not significant ($P > .05$). Final models were generated with nonsignificant factors dropped; there were negligible changes in AIC (median, 1.7; range, 0.5 to 7.0).[20] Log-binomial regression was used to provide estimates of the relative risks (RRs) for the predictors. When the log-binomial model did not converge (academics, behavioral rating, cognitive rating), logistic regression was used, and estimated odds ratios are presented as approximations to RRs. To examine the impact of chemotherapy on neurocognitive function, similar analyses were performed within the chemotherapy only group. Cumulative doses of IV and IT chemotherapy agents and history of oral agents (yes/no) were included. Chemotherapy drugs were grouped into classes: methotrexate, alkylating agents, other antimetabolites, corticosteroids, anthracyclines, vinca alkaloids, and topoisomerase inhibitors. For educational attainment and employment outcomes, college graduation versus no college graduation and full-time versus no full-time employment were modeled by using the eight neurocognitive impairment domains, current age, and sex as predictors. Model selection followed the same procedure employed for treatment effects except that Poisson models were used because of the high prevalence of education and employment outcomes.

RESULTS

Survivor Characteristics

On average, survivors were age 33 years and 26 years had passed since diagnosis; 32.8% were treated with 24-Gy CRT, 29.5% with 18 Gy, and 37.7% with chemotherapy only. More than 95% of survivors were treated on one of the SJCRH Total Therapy institutional protocols run at SJCRH since 1962 (for detailed discussion of these protocols, see Pui et al[21,22]). Current age, time since diagnosis, and treatment exposures differed across CRT groups because of changes in therapeutic approaches over time (Table 1). Of note, there were no significant differences between CRT groups in educational attainment or current employment.

Neurocognitive Outcomes

Rates of impairment ranged from 28.6% for self-reported behavior problems to 58.9% for direct assessment of executive function (Table 2). Rates of severe impairment increased as a function of CRT dose (Fig 1 and Table 3). Compared with the expected rate of 2% (predicted rate of healthy controls with z score of −2.0 or less; ie, two standard deviations below the age-based population mean), higher rates of severe impairment were noted in executive function (15.9%

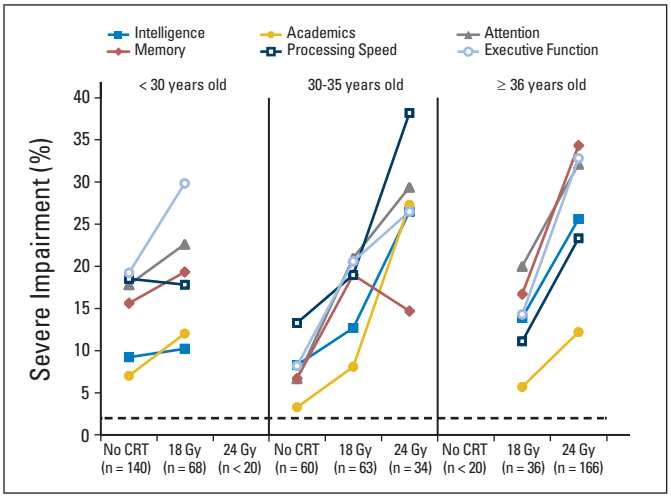

Fig 1. Percentage of survivors with severe impairment across eight domains of neurocognitive function. Rates are presented by treatment exposure (no cranial radiation therapy [CRT], 18-Gy CRT, and 24-Gy CRT) within three groupings of current age (< 30, 30 to 35, and ≥ 36 years old). No data are presented for the no-CRT group at ≥ 36 years of age and the 24-Gy CRT group at age younger than 30 years because of few survivors being in these cells. The dotted line at the bottom of the figure represents the expected level of severe impairment in the general population.

Table 3. Percent With Severe Neurocognitive Impairment by Treatment Exposure

Domain/Specific Ability	No CRT (n = 214)				18 Gy (n = 167)				24 Gy (n = 186)				
	Mean	SD	% Impairment	95% CI	Mean	SD	% Impairment	95% CI	Mean	SD	% Impairment	95% CI	P*
Intelligence			9.3	5.4 to 13.2			12.0	7.1 to 16.9			27.0	20.6 to 33.4	< .001
Full scale	0.0	0.9	3.7	1.2 to 6.3	–0.2	0.9	5.4	2.0 to 8.8	–0.5	1.1	10.3	5.9 to 14.7	< .001
Verbal	–0.2	1.1	7.5	4.0 to 11.0	–0.6	1.1	11.4	6.6 to 16.2	–0.8	1.2	21.0	15.1 to 26.8	< .001
Perceptual	0.1	0.9	5.1	2.2 to 8.1	0.1	0.9	3.6	0.8 to 6.4	–0.3	1.1	14.1	9.1 to 19.2	< .001
Academics			6.1	2.9 to 9.3			9.2	4.8 to 13.6			15.4	10.1 to 20.6	.002
Word reading	–0.2	0.6	2.3	0.3 to 4.4	–0.4	0.6	1.8	0.0 to 3.9	–0.6	0.8	6.0	2.6 to 9.5	< .001
Mathematics	–0.4	0.9	4.7	1.8 to 7.5	–0.6	0.9	8.6	4.3 to 12.9	–0.9	1.1	14.0	8.9 to 19.0	< .001
Attention			14.5	9.8 to 19.2			21.5	15.2 to 27.8			31.1	24.4 to 37.9	< .001
Focus	–0.1	1.2	8.4	4.7 to 12.1	–0.2	1.4	8.5	4.2 to 12.7	–0.4	1.5	14.1	9.0 to 19.1	.045
Sustain	–0.1	1.6	7.9	4.3 to 11.6	–0.6	2.6	12.8	7.7 to 17.9	–0.9	2.5	20.4	14.6 to 26.3	.003
Variability	–0.1	1.1	6.1	2.9 to 9.3	–0.4	1.3	10.4	5.7 to 15.0	–0.7	1.4	14.4	9.3 to 19.5	< .001
Memory			13.1	8.6 to 17.6			18.7	12.7 to 24.6			30.6	24.0 to 37.3	< .001
New learning	0.1	1.1	4.7	1.8 to 7.5	–0.2	1.2	8.4	4.2 to 12.7	–0.7	1.3	18.3	12.7 to 23.8	< .001
Short-term recall	0.0	1.1	9.3	5.4 to 13.2	–0.2	1.2	9.0	4.7 to 13.4	–0.7	1.3	16.1	10.8 to 21.4	< .001
Long-term recall	–0.1	1.1	6.5	3.2 to 9.9	–0.3	1.2	10.2	5.6 to 14.9	–0.7	1.4	18.8	13.2 to 24.4	< .001
Span	0.0	1.0	2.3	0.3 to 4.4	–0.3	1.0	5.4	2.0 to 8.8	–0.6	1.1	12.9	8.1 to 17.7	< .001
Processing speed			16.8	11.8 to 21.8			16.9	11.2 to 22.6			27.0	20.6 to 33.4	.013
Motor	–0.9	1.3	15.9	11.0 to 20.8	–0.9	1.3	16.9	11.2 to 22.6	–1.2	1.5	24.9	18.6 to 31.1	.11
Visual	0.1	1.0	3.3	0.9 to 5.7	–0.1	0.8	2.4	0.1 to 4.8	–0.6	1.0	10.3	5.9 to 14.6	< .001
Visual-motor	–0.1	1.0	1.9	0.1 to 3.7	–0.3	0.9	5.5	2.0 to 8.9	–0.7	0.9	9.2	5.0 to 13.4	< .001
Executive function			15.9	11.0 to 20.8			23.0	16.6 to 29.5			31.7	25.0 to 38.4	< .001
Flexibility	–0.5	1.7	14.0	9.4 to 18.7	–0.8	1.7	18.8	12.8 to 24.7	–1.2	1.9	26.5	20.1 to 32.8	< .001
Fluency	–0.3	0.9	5.6	2.5 to 8.7	–0.4	1.1	8.4	4.2 to 12.6	–0.8	1.0	15.6	10.4 to 20.8	< .001
Working memory	–0.2	0.9	0.5	0.0 to 1.4	–0.4	0.9	0.6	0.0 to 1.8	–0.5	0.9	2.7	0.4 to 5.0	< .001
Behavior rating			5.7	2.6 to 8.8			12.7	7.6 to 17.7			16.7	11.3 to 22.0	< .001
Inhibition	–0.1	1.0	4.7	1.9 to 7.6	–0.1	1.1	7.8	3.7 to 11.9	–0.2	1.0	6.5	2.9 to 10.0	.30
Shift	–0.1	1.1	6.6	3.3 to 10.0	–0.4	1.2	10.8	6.1 to 15.6	–0.7	1.3	17.2	11.8 to 22.6	< .001
Emotional control	–0.1	1.2	6.2	2.9 to 9.4	–0.5	1.3	14.5	9.1 to 19.8	–0.7	1.3	17.7	12.3 to 23.2	< .001
Self-monitor	0.1	1.1	4.7	1.9 to 7.6	–0.1	1.2	8.4	4.2 to 12.7	–0.3	1.2	7.5	3.7 to 11.3	.004
Cognitive rating			7.6	4.0 to 11.2			9.6	5.1 to 14.1			11.8	7.2 to 16.5	.15
Initiation	0.0	1.0	3.3	0.9 to 5.7	–0.2	1.1	6.6	2.8 to 10.4	–0.4	1.3	10.8	6.3 to 15.2	.001
Working memory	–0.5	1.3	13.7	9.1 to 18.4	–0.7	1.4	21.1	14.9 to 27.3	–1.1	1.4	30.6	24.0 to 37.3	< .001
Planning	–0.1	1.0	6.2	2.9 to 9.4	–0.2	1.2	7.2	3.3 to 11.2	–0.4	1.2	10.8	6.3 to 15.2	.007
Task completion	–0.1	1.1	4.7	1.9 to 7.6	–0.2	1.2	7.2	3.3 to 11.2	–0.5	1.3	10.2	5.9 to 14.6	.002
Organization	–0.1	1.1	7.1	3.6 to 10.6	–0.1	1.1	4.8	1.6 to 8.1	–0.4	1.1	7.0	3.3 to 10.7	.011

NOTE. Mean and SD are represented in age-adjusted *z* scores, referenced to nationally representative norms. Percent impairment is defined as age-adjusted *z* score of −2.0 or less.

Abbreviations: CRT, cranial radiation therapy; SD, standard deviation.

*Group *P* value from Cochran-Mantel-Haenszel χ^2 test of linear association comparing rates of impairment for domains, and group *P* values comparing mean standardized scores for specific abilities.

for no CRT to 31.7% for 24-Gy CRT), attention (14.5% to 31.1%), and memory (13.1% to 30.6%).

In multivariable models (Table 4), the impact of CRT was dependent on age at diagnosis. Compared with the no-CRT group, survivors had increased risk for intelligence impairment after 24-Gy CRT ($P < .001$), academic impairment after 24-Gy CRT ($P = .003$) or 18-Gy CRT ($P = .01$), and memory problems after 24-Gy CRT ($P < .001$). In all cases, risk was modified by age at diagnosis (Fig 2A; associated CIs are presented in Appendix Table A2, online only). Female sex increased risk for impaired intelligence ($P = .02$) and academics ($P < .001$). Females also demonstrated higher risk for impaired processing speed, although only after treatment with 24-Gy CRT ($P < .001$; Table 4).

Risk for certain neurocognitive impairment increased with time from diagnosis. Compared with the no-CRT group, survivors treated with 24-Gy CRT demonstrated increased risk for impaired executive function with increasing years from diagnosis (Fig 2B; Appendix Table A3, online only). Risk for impaired executive function 45 years after diagnosis was more than six-fold for survivors treated with 24-Gy CRT compared with the no-CRT group. CRT dose did not have an impact on patient-reported outcomes (PROs), although risk for self-reported behavior problems increased by 5% with each year from diagnosis across all groups.

Chemotherapy also had a direct impact on neurocognitive function. IV methotrexate increased the risk for slowed processing speed by 3% for each 1 g/m^2, controlling for cranial radiation (Table 4). Among the 214 survivors treated only with chemotherapy, increased rates of impairment were observed in all domains (all *P* values < .006). Multivariable models (Appendix Table A4, online only) revealed that dexamethasone exposure was associated with increased risk for

Table 4. Multivariable Regression Models Predicting Domains of Neurocognitive Impairment

Parameters	Intelligence			Academic			Attention			Memory		
	RR	95% CI	*P*	OR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*
CRT, Gy												
None	1.0			1.0			1.0			1.0		
18	1.46	0.46 to 4.60	.52	8.13	1.67 to 39.59	.01	1.48	0.96 to 2.30	.08	2.05	0.86 to 4.86	.11
24	6.63	2.54 to 17.27	< .001	8.56	2.08 to 35.26	.003	2.15	1.46 to 3.18	< .001	5.04	2.33 to 10.94	< .001
Age at diagnosis (years)*	—			—			—			—		
Age at diagnosis by CRT, Gy												
None	—†			—†			—			—†		
18	—†			—†			—			—†		
24	—†			—†			—			—†		
Time since diagnosis (per 1 year)*	—			—			—			—		
Time since diagnosis by CRT, Gy												
None	—			—			—			—		
18	—			—			—			—		
24	—			—			—			—		
Sex												
Male	1.0			1.0			—			—		
Female	1.61	1.10 to 2.36	.02	3.62	1.86 to 7.04	< .001	—			—		
Sex by CRT, Gy												
Male												
None	—			—			—			—		
18	—			—			—			—		
24	—			—			—			—		
Female												
None	—			—			—			—		
18	—			—			—			—		
24	—			—			—			—		
IV methotrexate (1 g/m^2)	—			—			—			—		

Processing Speed			Executive Function			Behavior Rating			Cognitive Rating		
RR	95% CI	*P*	RR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
1.0			1.0			1.0			1.0		
1.05	0.60 to 1.83	.86	1.62	0.22 to 11.77	.63	1.83	0.91 to 3.70	.09	2.66	0.96 to 7.35	.06
1.09	0.64 to 1.86	.75	0.46	0.07 to 2.90	.41	1.72	0.78 to 3.80	.18	0.86	0.24 to 3.11	.82
—			—			—			—		
—			—			—			—		
—			—			—			—		
—			—			—			—		
—			—			1.05	1.01 to 1.09	.03	—		
—			—†			—			—		
—			—†			—			—		
—			—†			—			—		
—			—			—			—		
—			—			—			—		
1.0			—			—			1.0		
1.47	0.77 to 2.81	.24	—			—			2.66	0.96 to 7.35	.06
1.57	0.83 to 2.97	.16	—			—			0.86	0.24 to 3.11	.82
1.0			—			—			1.0		
1.19	0.54 to 2.64	.67	—			—			0.60	0.22 to 1.67	.33
3.25	1.68 to 6.30	< .001	—			—			1.95	0.97 to 3.91	.06
1.03	1.00 to 10.6	.03	—			—					

NOTE. ORs were used instead of RRs for academic, behavioral rating, and cognitive rating outcomes because of lower frequency of severe impairment on these outcomes. (—) Indicates variables that were not retained in the models based on Akaike information criterion.

Abbreviations: CRT, cranial radiation therapy; IV, intravenous; OR, odds ratio; RR, relative risk.

*Represented as a continuous variable; effect indicates increased risk with each year.

†Significant risk based on interaction between age at diagnosis or time since diagnosis and cranial radiation dose.

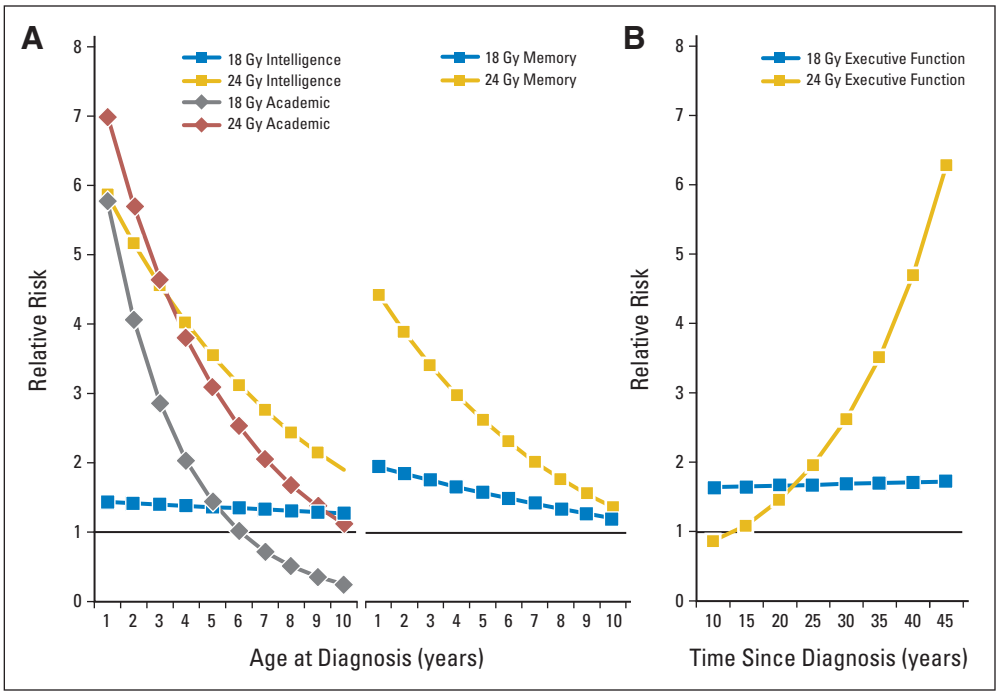

Fig 2. (A) Relative risk for severe neurocognitive impairment in academic skills and memory by age at diagnosis and dose of cranial radiation therapy (CRT). (B) Relative risk for severe neurocognitive impairment in executive function by time since diagnosis and dose of CRT. For each dose grouping of CRT (18 Gy or 24 Gy), relative risk is calculated in reference to the no-CRT group, which is represented by the solid back horizontal line.

impairment in attention (RR, 2.12; 95% CI, 1.11 to 4.03) and executive function (RR, 2.42; 95% CI, 1.20 to 4.91). IT hydrocortisone also increased risk for attention problems (RR, 1.24; 95% CI, 1.05 to 1.46). The risk for PROs was not increased by chemotherapy.

Educational Attainment and Employment

Adjusting for current age and sex, neurocognitive impairment was associated with educational attainment and employment. Risk for not graduating from college was associated with impaired intellect (RR, 1.33; 95% CI, 1.18 to 1.49), academics (RR, 1.28; 95% CI, 1.14 to 1.44), executive function (RR, 1.21; 95% CI, 1.04 to 1.41), and self-reported behavior problems (RR, 1.18; 95% CI, 1.07 to 1.31). College graduation was attained by less than 10% of survivors with severe intellectual or academic problems. Increased risk for not maintaining full-time employment was associated with impairment in intellect (RR, 1.42; 95% CI, 1.10 to 1.84), academics (RR, 1.31; 95% CI, 1.01 to 1.68), attention (RR, 1.29; 95% CI, 1.02 to 1.64), processing speed (RR, 1.31; 95% CI, 1.01 to 1.70), and self-reported cognitive problems (RR, 1.51; 95% CI, 1.22 to 1.85). Female sex was associated with increased risk for unemployment (RR, 1.33; 95% CI, 1.06 to 1.66), and older current age was associated with decreased risk (RR, 0.98 per year of age; 95% CI, 0.96 to 0.99). Although the ALL survivors demonstrated neurocognitive impairments, overall their educational attainment and employment status was remarkably similar to age- and sex-adjusted expected proportions using census data for the US population (data not shown).

DISCUSSION

Here we report direct neurocognitive assessment and PROs in the largest cohort of adult survivors of childhood ALL studied to date. At 26 years after diagnosis, survivors demonstrated increased rates of impairment in most neurocognitive and behavioral domains. The current data demonstrate several important novel findings: (1) impairment was common in survivors treated with lower doses of CRT and in those treated with chemotherapy only; (2) impairment in executive function skills increased with time since diagnosis; (3) impairment in intellect, academics, and memory progressively increased with younger age at treatment in a CRT dose-dependent manner; and (4) neurocognitive impairment was related to functional outcomes as adults, including college graduation and full-time employment.

One of the more significant outcomes was the increased risk for executive function impairments with increased time since diagnosis. This pattern may result from several processes. First, executive functions develop throughout adolescence and well into adulthood, and early injury may alter the trajectory of development such that skills lag farther behind with passing years.[23-25] In addition, survivors are at increasing risk for chronic health conditions as they age,[26] and health conditions can have an impact on executive function.[27] In this regard, time since diagnosis was also associated with increased risk for self-reported behavioral problems.

Age at treatment influenced the impact of CRT on neurocognitive functions. Consistent with previous literature based exclusively on PROs,[28] younger age at treatment with 24-Gy CRT increased risk for impairment in intelligence, academics, and memory. Importantly, there was not a clear demarcation of age at which CRT became less problematic. Rather, risk gradually decreased with increasing age. Because CRT exposure for ALL has an impact on all brain regions, it is not surprising that global brain exposure increases risk to skills that evolve in early childhood (eg, academics and memory).

Current results suggest the degree of impairment (ie, mild, moderate, or severe) demonstrates dose-response patterns. Survivors treated with 24-Gy CRT demonstrated the highest rates of impairment and the

highest number of domains that were severely impaired, though some abilities appeared to be more sensitive than others. Survivors demonstrated low rates of severe but high rates of mild working memory problems. High rates of severe impairment of complex neurocognitive processes such as flexibility and fluency were seen with 18-Gy CRT and after treatment with only chemotherapy. Working memory has often been viewed as being sensitive to cancer therapy.[29,30] The pattern of mild deficits in working memory in adulthood may suggest long-term recovery of basic skills at the expense of more complex abilities.

Interestingly, although groups treated with no CRT and those treated with 18-Gy CRT both demonstrated increased rates of impairment in all neurocognitive domains, few differences between these groups were noted. Compared with the no-CRT group, those treated with 18-Gy CRT had increased risk only for academic problems, and this risk was influenced by age at diagnosis. Concerns regarding neurocognitive impairment, multiple endocrinopathies, and development of secondary cancer have led to successful omission of CRT in all patients in some recent clinical trials.[21,31] However, as demonstrated in this study, treatment with chemotherapy only can also induce high rates of impairment in neurocognitive domains. Again, executive function, attention, memory, and processing speed demonstrated the highest rates of severe impairment. Both IV and IT methotrexate have been associated with neurocognitive impairment over brief follow-up intervals.[32] Our results demonstrate associations with dexamethasone chemotherapy, controlling for methotrexate exposure. Dexamethasone has increased CNS penetrance compared with prednisone,[33] and we have recently demonstrated associations between dexamethasone and altered functional magnetic resonance imaging activity in neural networks.[34] Future studies should consider the neurocognitive impact from various chemotherapy agents used in modern protocols, including agents not previously thought to be associated with neurocognitive morbidities.

Treatment had an impact on both neurocognitive testing and PROs, although direct assessment appeared to be more sensitive and specific to factors known to influence outcomes. Rates of executive dysfunction were higher for direct assessment, suggesting possible long-term adaptation in some adult survivors, or a lack of insight into the presence and impact of their behavior on their environment. PROs were not related to treatment dose or age at treatment. This increased sensitivity of direct assessment is consistent with results reported in other medical populations,[35,36] and it stresses the need to consider multimethod assessments for childhood cancer survivors. Medical professionals are encouraged to use direct assessment and not rely exclusively on patient reporting, which may underestimate problems in long-term survivors.

This study is not without limitations. It was not feasible to recruit controls, and nationally standardized neurocognitive measures with age-adjusted norms were used. Primary analyses were conducted between groups defined by treatment exposure, thereby accounting for the experience of growing up as a cancer survivor. These comparisons do limit the power to examine effects at distant times since diagnosis, given the fact that fewer survivors were treated with no CRT as many as 35 years ago. It was also not possible to adjust for potential differences in baseline socioeconomic status. In neurocognitive outcome studies with children, adjustment is accomplished by using parental education and occupation levels. However, parents did not accompany the adult survivors in this study, and survivor recall of parent occupation and education appeared to be related to survivor cognitive limitations. Finally, the three groups of survivors were treated during different historical periods with different durations from diagnosis. This pattern reflects the gradual transition from 24-Gy CRT in the 1960s and 1970s, to 18-Gy CRT in the 1980s and 1990s, to greater reliance on chemotherapy in recent decades. Even within the no-CRT group, doses and variability of chemotherapy agents used to treat children 21 years ago (the mean time since diagnosis in this group) may not reflect current treatment regimens.

These limitations notwithstanding, the current results suggest that survivors of childhood leukemia experience high rates of severe and pervasive neurocognitive impairment well into adulthood. Although survivors appear to adapt to some of these difficulties, deficits continue to have significant impact on their psychosocial functioning. Ongoing services to support survivors of childhood cancer are needed as they transition into adulthood. Resources for success in higher education and vocational placement may improve this transition and future quality of life. Continued monitoring by health professionals is recommended to identify neurocognitive problems that may emerge with time. Treatment of these problems may enhance long-term maturation and quality of life.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

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GLOSSARY TERM

Akaike information criterion: Measure of the goodness of fit of a statistical model that discourages overfitting and is used as a tool for model selection. For a given data set, competing models are ranked according to their Akaike information criterion value, and the one with the lowest value is considered the best. However, there is no established value above which a given model is rejected.

Appendix

Table A1. Comparison Between Eligible Participants and Nonparticipants

Characteristic	Eligible Participants (n = 567)		Nonparticipants (n = 276)		*P*
	No.	%	No.	%	
Sex					.02
Female	297	52.4	121	43.8	
Male	270	47.6	155	56.2	
Race/ethnicity					.64
White	523	92.2	252	91.3	
Other	44	7.8	24	8.7	
CRT, Gy					.82
None	214	37.7	110	39.9	
18	167	29.5	77	27.9	
24	186	32.8	89	32.2	
Decade of diagnosis					.60
1960-69	26	4.6	15	5.4	
1970-79	150	26.5	65	23.6	
1980-89	272	48.0	129	46.7	
1990-99	119	21.0	67	24.3	
Current age, years					.50
18-29	204	36.0	94	34.1	
30-39	229	40.4	123	44.6	
40-58	134	23.6	59	21.4	
Age at diagnosis, years					.81
Mean	6.6		6.5		
SD	4.4		4.4		
Median	5.1		5.1		
Range	0.2-18.8		0.03-20.0		

Abbreviations: CRT, cranial radiation therapy; SD, standard deviation.

Table A2. RRs and 95% CIs for Neurocognitive Impairment by CRT and Age at Diagnosis

Age at Diagnosis (years)	CRT (Gy)	Intelligence		Academic		Memory	
		RR	95% CI	RR	95% CI	RR	95% CI
1	18	1.44	0.51 to 4.08	5.75	1.50 to 22.01	1.94	0.89 to 4.23
	24	5.85	2.47 to 13.83	6.99	2.03 to 24.04	4.42	2.22 to 8.82
2	18	1.42	0.55 to 3.64	4.06	1.31 to 12.63	1.84	0.92 to 3.70
	24	5.16	2.39 to 11.13	5.70	1.96 to 16.62	3.88	2.10. 7.16
3	18	1.40	0.60 to 3.27	2.87	1.08 to 7.63	1.75	0.94 to 3.26
	24	4.55	2.29 to 9.03	4.65	1.84 to 11.75	3.40	1.97 to 5.86
4	18	1.38	0.65 to 2.96	2.03	0.83 to 5.00	1.65	0.94 to 2.90
	24	4.02	2.18 to 7.40	3.80	1.68 to 8.59	2.98	1.83 to 4.86
5	18	1.36	0.69 to 2.71	1.44	0.57 to 3.62	1.57	0.94 to 2.62
	24	3.54	2.04 to 6.16	3.10	1.45 to 6.60	2.62	1.67 to 4.10
6	18	1.35	0.72 to 2.52	1.02	0.36 to 2.87	1.49	0.92 to 2.41
	24	3.13	1.87 to 5.23	2.53	1.19 to 5.38	2.30	1.49 to 3.54
7	18	1.33	0.73 to 2.40	0.72	0.21 to 2.44	1.41	0.88 to 2.27
	24	2.76	1.67 to 4.56	2.06	0.91 to 4.67	2.01	1.29 to 3.14
8	18	1.31	0.73 to 2.34	0.51	0.12 to 2.16	1.34	0.82 to 2.19
	24	2.43	1.45 to 4.08	1.68	0.67 to 4.25	1.77	1.10 to 2.84
9	18	1.29	0.71 to 2.34	0.36	0.07 to 1.96	1.27	0.75 to 2.15
	24	2.15	1.23 to 3.74	1.37	0.47 to 4.00	1.55	0.91 to 2.62
10	18	1.27	0.67 to 2.41	0.25	0.04 to 1.81	1.20	0.67 to 2.16
	24	1.90	1.03 to 3.50	1.12	0.33 to 3.86	1.36	0.75 to 2.46

NOTE. Risk associated with CRT is referenced to no-CRT group.
Abbreviations: CRT, cranial radiation therapy; RR, relative risk.

Table A3. RRs and 95% CIs for Neurocognitive Impairment by CRT and Time Since Diagnosis

		Executive Function	
Time Since Diagnosis (years)	CRT (Gy)	RR	95% CI
10	18	1.65	0.57 to 4.80
	24	0.87	0.28 to 2.70
15	18	1.66	0.77 to 3.57
	24	1.10	0.45 to 2.71
20	18	1.67	1.02 to 2.72
	24	1.47	0.75 to 2.91
25	18	1.68	1.00 to 2.83
	24	1.97	1.08 to 3.61
30	18	1.70	0.74 to 3.88
	24	2.64	1.28 to 5.43
35	18	1.71	0.51 to 5.77
	24	3.53	1.34 to 9.27
40	18	1.72	0.34 to 8.80
	24	4.72	1.33 to 16.70
45	18	1.73	0.22 to 13.54
	24	6.31	1.29 to 30.85

NOTE. Risk associated with CRT is referenced to no-CRT group.
Abbreviations: CRT, cranial radiation therapy; RR, relative risk.

Table A4. Multivariable Regression Models Predicting Domains of Neurocognitive Impairment in No-CRT Group

Parameters	Intelligence				Academic				Attention				Memory			
	Beta	RR	95% CI	*P*	Beta	OR	95% CI	*P*	Beta	RR	95% CI	*P*	Beta	RR	95% CI	*P*
Age at diagnosis (years)*	—	—		—	—	—		—	—	—		—	—	—		—
Time since diagnosis (per 1 year)*	—	—		—	—	—		—	—	—		—	−0.08	0.92	0.85 to 0.99	.03
Females	—	—		—	—	—		—	—	—		—	—	—		—
IT methotrexate (per 50 mL)	—	—		—	—	—		—	—	—		—	—	—		—
IV methotrexate (per 1 g/m^2)	—	—		—	−0.06	0.94	0.87 to 1.01	.10	—	—		—	—	—		—
IT hydrocortisone (per 100 mL)	—	—		—	—	—		—	0.21	1.24	1.05 to 1.46	.01				
Dexamethasone (yes/no)	0.76	2.13	0.90 to 5.01	.08	—	—		—	0.75	2.12	1.11 to 4.03	.02	—	—		—
Anthracyclines	—	—		—	—	—		—	—	—		—	—	—		—
Alkylating agents	—	—		—	—	—		—	—	—		—	—	—		—
Vinca alkaloids	—	—		—	—	—		—	—	—		—	−0.02	0.98	0.96 to 1.00	.02
Topoisomerase inhibitors	—	—		—	—	—		—	—	—		—	—	—		—

Processing Speed				Executive Function				Behavior Rating				Cognitive Rating			
Beta	RR	95% CI	*P*	Beta	RR	95% CI	*P*	Beta	OR	95% CI	*P*	Beta	OR	95% CI	*P*
—	—		—	—	—		—	—	—		—	—	—		—
−0.07	0.93	0.88 to 0.99	.03	—	—		—	—	—		—	—	—		—
—	—		—	—	—		—	—	—		—	—	—		—
—	—		—	—	—		—	—	—		—	−0.69	0.50	0.30 to 0.84	.009
—	—		—	−0.05	0.95	0.92 to 1.00	.03	—	—		—	—	—		—
−0.22	0.80	0.66 to 0.97	.02												
—	—		—	0.89	2.42	1.20 to 4.91	.01	—	—		—	—	—		—
—	—		—	—	—		—	—	—		—	−0.76	0.47	0.12 to 1.88	.29
—	—		—	—	—		—	—	—		—	—	—		—
—	—		—	—	—		—	−0.05	0.95	0.91 to 1.00	.05	—	—		—
0.05	1.05	1.01 to 1.10	.03	—	—		—	0.10	1.11	0.95 to 1.28	.19	—	—		—

NOTE. Odds ratios (ORs) were used instead of relative risks (RRs) for academic, behavior rating, and cognitive rating outcomes because of lower frequency of impairment on these outcomes. (—) Indicates variables that were not retained in the models based on Akaike information criterion.

Abbreviations: CRT, cranial radiation therapy; IT, intrathecal; IV, intravenous.

*Represented as a continuous variable; effect indicates increased risk with each year.